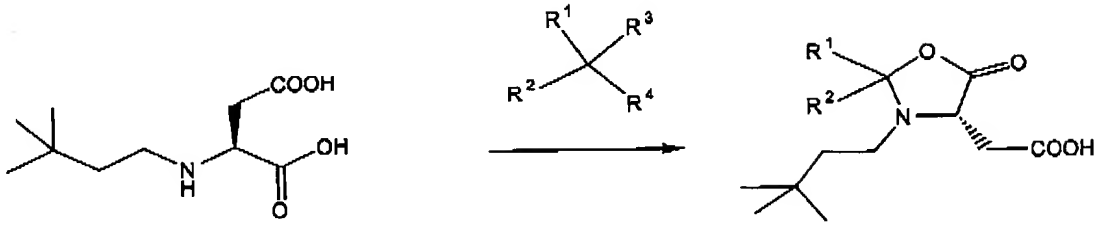
In the Specification:

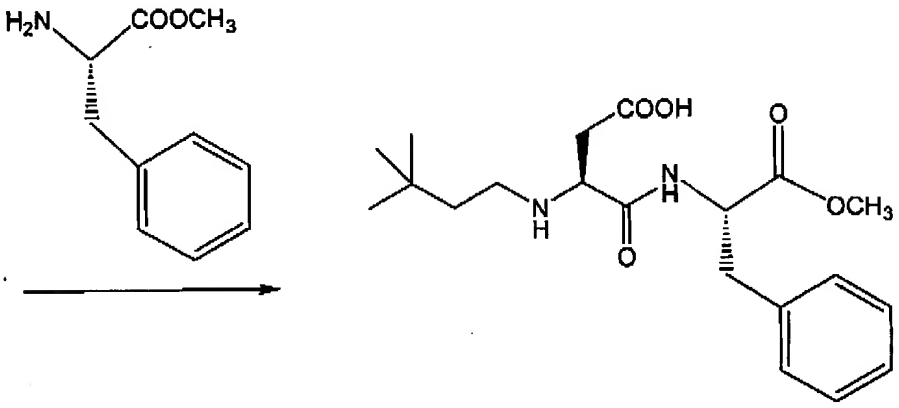
Please replace the paragraphs starting at page 5, line 1, and ending at page 7, line 16, with the following replacement paragraphs:

~~1~~ According to the present inventive method, neotame is synthesized by reacting N-(3,3-dimethylbutyl)-L-aspartic acid and a ketone in a solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative and by reacting the oxazolidinone derivative and phenylalanine or phenylalanine methyl ester in the solvent for a time and at a temperature sufficient to produce N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

The present invention relates to the regioselective formation of N-alkylated α-aspartyl amides via the use of ketones, and particularly to the use of such regioselective processing to obtain oxazolidinone derivatives which can react with L-phenylalanine methyl ester in a solvent with or without acid and/or a catalyst to yield N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester (neotame) with the usual work-up. The present synthetic method is represented by the following reaction scheme:



wherein R^1 is R^2, R^2 is Ph or CX_3, X is H, Cl, Br or F, R^3 and R^4 taken together is =O, or R^3 and R^4 are the same and are OCH_3 or OC_2H_5



According to the present invention, neotame is synthesized by reacting N-(3,3-dimethylbutyl)-L-aspartic acid and a ketone in a first solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative and by reacting the

C1

oxazolidinone derivative and phenylalanine or phenylalanine methyl ester in a second solvent for a time and at a temperature sufficient to produce N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

According to the first step of the present inventive method, an admixture of N-(3,3-dimethylbutyl)-L-aspartic acid and a ketone are reacted in a first solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative.

Ketones of the formula $R^1R^2C=O$ or acetals of ketones of the formula $CR^1R^2R^3R^4$, wherein R^1 is R^2, R^2 is Ph or CX_3, X is H, Cl, Br or F, R^3 and R^4 taken together is =O, or R^3 and R^4 are the same and are OCH_3 or OC_2H_5 are suitable for use in the present invention. Ph is phenyl or substituted phenyl. Suitable ketones include, without limitation, hexafluoroacetone, 1,1,1-trifluoroacetone, hexachloroacetone, and combinations thereof.

N-(3,3-dimethylbutyl)-L-aspartic acid is prepared as described in U.S. Patent No. 6,077,962, the disclosure of which is incorporated by reference herein. The ketones are readily available starting materials. The N-(3,3-dimethylbutyl)-L-aspartic acid and the ketone are typically combined in a molar ratio ranging from about 1:1 to about 1:4.--

C1

A marked-up copy of these paragraphs, showing the changes made thereto, is attached.

Please replace the paragraph at page 8, lines 1-11, with the following replacement paragraph:

In certain embodiments of the present invention, a catalyst may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the ketone. Suitable catalysts include, without limitation, p-toluenesulfonic acid. In certain embodiments of the present invention, an acid may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the ketone. Suitable acids include, without limitation, formic acid, acetic acid, p-toluenesulfonic acid, methane sulfonic acid, 10-camphorsulfonic acid and combinations thereof.

C2

A marked-up copy of this paragraph, showing the changes made thereto, is attached.

Please delete the paragraphs starting at page 13, line 14, and ending at page 14, line 22, have been deleted.

Please replace the paragraphs starting at page 14, line 24, and ending at page 16, line 3, with the following replacement paragraphs:

EXAMPLE 3

2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid

A gas flow of hexafluoroacetone is blown at a moderate rate at room temperature onto an intensely stirred suspension of 10 mmol of N-(3,3-dimethylbutyl)-L-aspartic acid in 20 ml 1,4-dioxane. A clear solution is formed overnight. The solvent was removed in vacuo, and

C3

the oily residue was confirmed to be an almost quantitative amount of 2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid by NMR.

EXAMPLE 4

N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester

2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid (2 mmol) and L-phenylalanine 1-methyl ester (2 mmol) were dissolved in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo to yield an oil. A white solid, confirmed to be neotame by NMR, was obtained after stirring the oil in water overnight. Neotame was obtained in 90% yield.

EXAMPLE 5

N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester

L-phenylalanine 1-methyl ester hydrochloride (10 mmol), tetrahydrofuran (15 ml) and sodium acetate (NaOAc, 10 mmol) were loaded into a 50 ml flask. The mixture was stirred at room temperature for 15 minutes. A solution of 2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid (10 mmol) in tetrahydrofuran (10 ml) was added to the mixture. The mixture was then stirred at room temperature for 24 hours. The solvent was removed in vacuo to yield a residue. The residue was stirred in water overnight at room temperature. The precipitated solid was filtered, washed with water and dried to yield neotame in 90% yield.

C 3